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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/048,046	01/24/2002	Thanos Halazonetis	WST 97AUSA	2775

270 7590 06/04/2004

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 06/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/048,046	HALAZONETIS ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42* is/are pending in the application.

4a) Of the above claim(s) *7-20,24,26,28-31 and 33-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,21-23,25,27 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/3/02;10/9/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election without traverse of group I, Claims 1-6, 21-23, 25, 27, 32 in Paper of 03/11/04 is acknowledged and entered.

Claims 1-42 are pending in the instant application and Claims 7-20, 24, 26, 28-31, 33-42 have been withdrawn from further consideration by the Examiner under 37 CFR 1.142(b) as being drawn to non-elected invention.

Group I, Claims 1-6, 21-23, 25, 27, 32 are currently under prosecution.

OBJECTION

1. Claims 1, 21, 23, 25 are objected to for the use of the language "associated". It is not clear what kind of association is referred to.

2. Claims 21, 23 are objected to because it is not clear that the recited "diagnostic agent" is for diagnosing of what.

3. Claim 23 is objected to because part of claim 23 is drawn to non-elected invention, i.e. a diagnostic reagent comprising a "polypeptide ligand" which binds to Chfr.

4. Claim 25 is objected to because part of claim 23 is drawn to non-elected invention, i.e. a diagnostic kit comprising a "polypeptide ligand" which binds to Chfr.

5. Claims 27, 32 are objected to because part of claims 27, 32 is drawn to non-elected invention, i.e. an inhibitor which is not a polynucleotide or antisense inhibitor, for example, a polypeptide or peptide or antibody inhibitor of the biological activity of Chfr.

6. Claim 32 is objected to because claim 32 depends on non-elected claim 32.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

Claims 21-23, 25 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claims 21-23, 25 are drawn to :

1) A diagnostic reagent comprising a nucleotide sequence that "binds" to the Chfr nucleic acid sequence or a fragment thereof, or a ligand that "binds" to Chfr (claims 21, 23, 25). Said polynucleotide reagent is an antisense fragment of SEQ ID NO:1 or a fragment of SEQ ID NO:1 (claim 22).

It is noted that a nucleotide sequence that "binds" to the chfr nucleic acid sequence or a fragment thereof, or a ligand that "binds" to Chfr encompasses unrelated sequences that binds to the chfr nucleic acid sequence or a fragment thereof, via a common antisense fragment of SEQ ID NO:1 or a fragment of SEQ ID NO:1.

It is further noted that a chfr nucleic acid sequence encompasses variants of SEQ ID NO:1 or a fragment thereof with unknown structure, in view of the disclosure in the specification that chfr is not limited solely to the nucleotide sequences presented in the instant specification, but includes any and all nucleotide sequences which share homology with the nucleotide sequences presented in the instant specification,

preferably having 70%, 75%, 80% 85% , 90%, 95% or 99% identity with SEQ ID NO: 1 or a fragment thereof (p.9, last paragraph, bridging p.10).

In addition, it is noted that a nucleotide sequence which binds to the chfr nucleic acid sequence and which "is" an antisense fragment of SEQ ID NO:1 or a fragment of SEQ ID NO:1 is interpreted as an open language, i.e. a nucleotide sequence "comprising" an antisense fragment of SEQ ID NO:1 or a fragment of SEQ ID NO:1, wherein said nucleotide sequence could have any sequences attached to an antisense fragment or a fragment of SEQ ID NO:1. There is no limitation as to the nature of the molecules attached to an antisense fragment or a fragment of SEQ ID NO:1. The present claim encompasses full-length genes and cDNAs that are not further described.There is substantial variability among the species of DNAs encompassed within the scope of the claims because an antisense fragment or a fragment of SEQ ID NO:1 is only a fragment of any full-length gene or cDNA species. "A polynucleotide which is an antisense fragment or a fragment of SEQ ID NO:1" encompasses a variety of subgenera with widely varying attributes .For example,a cDNA 's principle attribute would include its coding region. A partial cDNA that did not include a disclosure of any open reading frame (ORF)of which it would be a part,would not be representative of the genus of cDNAs because no information regarding the coding capacity of any cDNA molecule would be disclosed.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the

application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, "requires a precise definition, such as by structure, formula, [or] chemical name," of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a

recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that the written description requirement can be met by show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here.

Thus, the instant specification may provide an adequate written description of a nucleotide sequence which "binds" to the chfr nucleic acid sequence, and which "is" an antisense fragment of SEQ ID NO:1 or a fragment of SEQ ID NO:1 or a ligand that "binds" to Chfr, or the chfr nucleic acid sequence, per Lilly by structurally describing a representative number of a nucleotide sequence which "binds" to the chfr nucleic acid sequence, and which "is" an antisense fragment of SEQ ID NO:1, or a ligand that "binds" to Chfr, or the chfr nucleic acid sequence or by describing "structural features common to the members of the genus, which features constitute a substantial portion of

the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe a nucleotide sequence which "binds" to the chfr nucleic acid sequence, and which "is" an antisense fragment of SEQ ID NO:1, or a ligand that "binds" to Chfr, or the chfr nucleic acid sequence in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any nucleotide sequence which "binds" to the chfr nucleic acid sequence, and which "is" an antisense fragment of SEQ ID NO:1, or a ligand that "binds" to Chfr, or the chfr nucleic acid sequence, other than SEQ ID NO:1, nor does the specification provide any partial structure of such a nucleotide sequence which "binds" to the chfr nucleic acid sequence, and which "is" an antisense fragment of SEQ ID NO:1, or a ligand that "binds" to Chfr, or the chfr nucleic acid sequence, nor any physical or chemical characteristics of a nucleotide sequence which "binds" to the chfr nucleic acid sequence , and which "is" an antisense fragment of SEQ ID NO:1, or a ligand that "binds" to Chfr, or the chfr nucleic acid sequence, other than SEQ ID NO:1, nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses a single polynucleotide of SEQ ID NO:1, this does not provide a description of a nucleotide sequence which "binds" to the chfr nucleic acid sequence, and which "is" an antisense

fragment of SEQ ID NO:1, or a ligand that "binds" to Chfr, or the chfr nucleic acid sequence that would satisfy the standard set out in Enzo.

The specification also fails to describe a nucleotide sequence which "binds" to the chfr nucleic acid sequence, and which "is" an antisense fragment of SEQ ID NO:1, or a ligand that "binds" to Chfr, or the chfr nucleic acid sequence by the test set out in Lilly. The specification describes only a single polynucleotide of SEQ ID NO:1. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of a nucleotide sequence which "binds" to the chfr nucleic acid sequence, and which "is" an antisense fragment of SEQ ID NO:1, or a ligand that "binds" to Chfr, or the chfr nucleic acid sequence that is required to practice the claimed invention.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

Claims 1-6, 21-23, 25, 27, 32 are rejected under 35 USC 112, first paragraph.

A. Claims 1-6, 21-23, 25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polynucleotide of SEQ ID NO:1, **does not reasonably provide enablement for 1) A nucleic acid sequence of a mitotic checkpoint gene, encoding a Chfr protein having a Forkhead-associated domain, and a Ring finger, wherein said protein is required for regulation of the transition of cells from prophase to metaphase, 2) A sequence of claim 1,**

encoding at least amino acids 31-103, and/or amino acids 303-346, and/or amino acids 476-641 of SEQ ID NO:2, 3) A sequence having a homology of at least 50% to SEQ ID NO:1, or a sequence of claim 1, encoding at least amino acids 31-103, and/or amino acids 303-346, and/or amino acids 476-641 of SEQ ID NO:2 according to a selected algorithm and encoding a protein or peptide having ubiquitin-protein ligase activity, 4) a nucleotide sequence or a ligand which binds to the chfr nucleic acid sequence, or a fragment thereof, and which is an antisense fragment of SEQ ID NO:1 or a fragment of SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 1-6, 21-23, 25 are drawn to:

1) A nucleic acid sequence of a mitotic checkpoint gene, encoding a Chfr protein having a Forkhead-associated domain, and a Ring finger, wherein said protein is required for regulation of the transition of cells from prophase to metaphase (claims 1-6),

2) A sequence of claim 1, encoding at least amino acids 31-103, and/or amino acids 303-346, and/or amino acids 476-641 of SEQ ID NO:2 (claim 2),

3) A sequence having a homology of at least 50% to SEQ ID NO:1, or a sequence of claim 1, encoding at least amino acids 31-103, and/or amino acids 303-346, and/or amino acids 476-641 of SEQ ID NO:2 according to a selected algorithm and encoding a protein or peptide having ubiquitin-protein ligase activity (claim 2), and

4) A nucleotide sequence or a ligand which binds to the chfr nucleic acid sequence, or a fragment thereof, and which "is" an antisense fragment of SEQ ID NO:1 (claims 21-23, 25).

The specification discloses that chfr according to this invention is not limited solely to the nucleotide sequences presented in the instant specification, but includes any and all nucleotide sequences which share homology with the nucleotide sequences presented in the instant specification, preferably having 70%, 75%, 80% 85% , 90%, 95% or 99% identity with SEQ ID NO: 1 or a fragment thereof (p.9, last paragraph, bridging p.10).

The specification further discloses 1) a forkhead-associated DNA-binding domain (FHA) of the claimed chfr, which was initially identified in transcriptional factors, and in protein kinases (p.8, lines 2-5), 2) a ring finger (RF) motif of the claimed chfr, which is similar to that of a virus transactivator, wherein the virus transactivator interacts with the kinetochore and interfere with progress through mitosis, the two activities that require an intact ring finger (p.34, lines 10-14). The specification discloses that all three fragments, the FHA domain, the ring finger and the cysteine rich domain are necessary for Chfr to have biological activity, such as the ability to delay entry into metaphase (p.13, lines 13-16).

It is noted that a nucleic acid sequence of a mitotic checkpoint gene, encoding a Chfr protein having a Forkhead-associated domain, and a Ring finger, wherein said protein is required for regulation of the transition of cells from prophase to metaphase,

encompasses nucleic acid variants of SEQ ID NO:1, with unknown structure, provided they have a Forkhead-associated domain, and a Ring finger.

It is further noted that a polynucleotide encoding at least amino acids 31-103, and/or amino acids 303-346, and/or amino acids 476-641 of SEQ ID NO:2 encompasses a polynucleotide with unknown sequences attached to a sequence that encodes at least amino acids 31-103, and/or amino acids 303-346, and/or amino acids 476-641 of SEQ ID NO:2.

In addition, A sequence having a homology of at least 50% to SEQ ID NO:1, or a sequence of claim 1, encoding at least amino acids 31-103, and/or amino acids 303-346, and/or amino acids 476-641 of SEQ ID NO:2 according to a selected algorithm and encoding a protein or peptide having ubiquitin-protein ligase activity encompasses variants of SEQ ID NO:1 with unknown structure, or variants of fragments of SEQ ID NO:1, encoding at least amino acids 31-103, and/or amino acids 303-346, and/or amino acids 476-641 of SEQ ID NO:2.

Moreover, A nucleotide sequence or a ligand that binds to the chfr nucleic acid sequence encompasses unrelated nucleotide sequences with unknown structure and function that bind to the chfr nucleic acid sequence or SEQ ID NO:1 or a variant thereof, via a common fragment. In addition, a nucleotide sequence or a ligand that binds to a fragment of the chfr nucleic acid sequence encompasses a nucleotide sequence or a ligand that binds to an unrelated sequence, having a common fragment with the chfr nucleic acid sequence via which the claimed a nucleotide sequence or ligand binds. In other words, said detected fragment of the chfr nucleic acid sequence by the claimed a

nucleotide sequence ligand is not necessarily specific for the chfr nucleic acid sequence.

In addition, it is noted that a nucleotide sequence which binds to the chfr nucleic acid sequence and which "is" an antisense fragment of SEQ ID NO:1 or a fragment of SEQ ID NO:1 is interpreted as an open language, i.e. a nucleotide sequence "comprising" an antisense fragment of SEQ ID NO:1 or a fragment of SEQ ID NO:1, wherein said nucleotide sequence could have any sequences attached to an antisense fragment or a fragment of SEQ ID NO:1.

One cannot extrapolate the teaching in the specification to the scope of the claims. Applicant has not taught how to make the claimed polynucleotides such that they have function as claimed, e.g. encoding a polypeptide that regulates of the transition of cells from prophase to metaphase, or has ubiquitin protein ligase activity.

The following teaching of the art, although drawn to proteins, would apply as well the claimed polynucleotide variants of SEQ ID NO:4, because polynucleotide sequences encode proteins. It is well known in the art that protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, Bowie et al (Science, 1990, 257 : 1306-1310) teach that an amino acid sequence encodes a message that determine the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instruction of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely

complex (col.1, p.1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitution can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col.2, p.1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al, (Journal of Cell Biology, 1990, 11: 2129-2138), who teach that replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cell Biology, 1988, 8: 1247-1252). Similarly, it has been shown that aglycosylation of antibodies reduces the resistance of the antibodies to proteolytic degradation, while CH2 deletions increase the binding affinity of the antibodies (see Tao. et al. The Journal of Immunology, 1989, 143(8): 2595-2601, and Gillies et al. Human Antibodies and Hybridomas, 1990, 1(1): 47-54). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

In view of the teaching in the art, one cannot predict that polynucleotide sequence encoding a sequence with unknown structure attached to a Forkhead-associated domain, and a Ring finger domain, or a sequence that is 50% homologous to SEQ ID NO:1, or a polynucleotide with unknown sequences attached to a sequence that encodes at least amino acids 31-103, and/or amino acids 303-346, and/or amino acids 476-641 of SEQ ID NO:2 , or a polynucleotide with unknown sequences attached to an antisense fragment or a fragment of SEQ ID NO:1 would still have the conformation necessary for the claimed function of the polypeptide encoded by the claimed polynucleotide.

The specification however does not disclose how to make the claimed nucleic acid molecules, such that they would function or have the properties as claimed, or how to use said nucleic acid molecules if they did not have the function or properties claimed.

It is noted that although the specification discloses that all three fragments, the FHA domain, the ring finger and the cysteine rich domain are necessary for Chfr to have biological activity, such as the ability to delay entry into metaphase (p.13, lines 13-16), one cannot predict that the presence of these three fragments alone are sufficient for the claimed biological activity of SEQ ID NO:1, because the effect of unknown sequences attached to these three fragments on the function of the fragments and the full length sequence is not predictable. The specification however does not teach which amino acids of the polypeptide encoded by the claimed polynucleotide, besides the amino acids of the above three fragments, should not be substituted, deleted or added,

such that the polypeptide encoded by the claimed polynucleotide still retains the biological activity of SEQ ID NO:1. In addition, the specification does not teach the type of substitution besides conservative substitution, nor the type of amino acids replacing the original amino acids. Similarly, the specification does not teach the structure of the polynucleotide attached to a sequence that encodes at least amino acids 31-103, and/or amino acids 303-346, and/or amino acids 476-641 of SEQ ID NO:2, such that the polynucleotide encoding a polypeptide comprising said fragments still would have the conformation necessary for their function as claimed. Further, the specification does not teach how to make myriads of the claimed ligand polynucleotides that bind to SEQ ID NO:1 or a variant thereof, via a common fragment.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

B. If Applicant could overcome the above 112, first paragraph, claim 25 is still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a kit for detecting the presence of SEQ ID NO:1 comprising SEQ ID NO:1, **does not reasonably provide enablement for a diagnostic kit for detecting the tumorigenic potential of a cell**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

Claim 25 is drawn to a diagnostic kit, for detecting "the tumorigenic potential of a cell", comprising a nucleotide sequence that binds to the Chfr nucleic acid sequence or

a fragment thereof, or a ligand that binds to Chfr, said reagent associated with a detectable label, and further comprising suitable components for detection of said label.

Claim 25 encompasses a diagnostic for detecting risk of cancer.

The specification discloses that the Chfr checkpoint that regulates entry into metaphas is evident in primary normal human cells, but is inactivated in human cancer cell lines (p.45, second paragraph).The specification further discloses that cells that lack proper checkpoints in the cell cycle are more likely to develop into tumor cells (p.24, lines 13-14).

One cannot extrapolate the teaching in the specification to the scope of the claims. The specification provides neither guidance on nor exemplification of how to correlate the inactivation of SEQ ID NO:1 with tumorigenic potential of a cell, or risk of cancer. Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing an cancer biomarker (intermediate end point marker) to successful clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to SEQ ID NO:1 for detecting tumorigenic potential of a cell. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and **if validated** (emphasis added) can be used for population screening (p. 2713s, col 1). The reference further teaches that once

selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and link those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). Although the specification discloses an inactivation of SEQ ID NO:1 in human cancer cell lines, the specification does not disclose any correlation between tumorigenic potential or risk of cancer, and SEQ ID NO:1 as a prognostic marker. The specification has not shown that the patients with inactivation of SEQ ID NO:1 have tumorigenic potential or an increased risk of cancer over other patients. The specification has not shown that SEQ ID NO:1 has a predictive value for tumorigenic potential or risk of cancer in prospective population trials. In view of the above, undue experimentation would be required to practice the claimed invention.

C. If Applicant could overcome the above 112, first paragraph, claims 27, 32 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a full length antisense of SEQ ID NO:1, **does not reasonably provide enablement for a composition which inhibits the biological activity of**

Chfr or an inhibitor of Chfr. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims

Claim 27 is drawn to a composition which inhibits the biological activity of Chfr.

Claim 32 is drawn to an inhibitor of Chfr identified by the method of claim 31.

Claim 32 recites a product by process, and thus is treated as the product per se.

Claims 27, 32 encompass an inhibitor of SEQ ID NO:1, such as an antisense sequence of SEQ ID NO:1, which could inhibit the biological activity of SEQ ID NO:1 in vivo, such as in antisense or gene therapy.

The specification contemplates a therapeutic method for retarding growth of tumor cells, by inhibition of expression of Chfr in tumor cells, which would results in tumor cells that are more sensitive to mitotic stress, and thus more sensitive to agents such as nocodazole and taxol that disrupt microtubule function (p.28, second paragraph).

One cannot extrapolate the teaching in the specification to the claims, because it is unpredictable that the claimed composition or inhibitor of Chfr could inhibit the biological activity of SEQ ID NO:1 in vivo, in view that antisense and gene therapy is unpredictable. It is well known in the art that antisense therapy is unpredictable. Branch, AD, 1998, TIBS 23: 45-50 teaches that it is very difficult to predict what portions of an RNA molecule will be accessible to an antisense sequence *in vivo*, and therefore, rational design of antisense molecule is not possible. Branch further teaches that although antisense oligonucleotides could be screened *in vitro*, it is not clear whether

the identified antisense oligonucleotides are effective *in vivo*, and that *in vitro* studies will not always predict *in vivo* efficacy (p.49, first column, last paragraph, bridging second paragraph, and last column, second paragraph). In addition, Branch also teaches that although some antisense molecules had some clinical value through non-antisense effects, the non-antisense effects are not predictable and these effects must be explored on a case-by-case basis (p.50, first column). Further, even if an antisense oligonucleotide could be successfully used *in vitro* to inhibit the expression of a gene, it is unpredictable that said antisense oligonucleotide could be successfully used *in vivo*, because 1) successful application of antisense therapy *in vivo* has been extremely limited, and that there are only a few reports of modulation of various pathological conditions by antisense therapy in rodents, and 2) even if the biological significant amounts of antisense molecules reach target cells, and bind to selected target sites on mRNA, a subsequent effect on regulation of translation is not guaranteed, as taught by Weiss, 1998, US 5,840,708. Gura (Science, 1995, 270:575-577) discloses, as drawn to antisense therapy, that the biggest concern is that antisense compounds simply don't work the way researchers once thought they did, i.e. the antisense oligonucleotides do not always work by true antisense mechanisms, and could be pharmaceutically effective via unexpected non-antisense side effects and have the same effects as non-specific, control oligonucleotides (page 576) . In addition, Gura teaches that other drawbacks shown in animal studies include difficulty getting antisense oligonucleotides to target tissues and the existence of potentially toxic side effects such as increased blood clotting and cardiovascular problems (page 575, col 1, para 2). In addition, Gura reports

problems with synthetic antisense oligonucleotides in that unwanted and sometimes lethal side effects occurred in animal experiments, and that they block cell migration and adhesion to underlying tissue *in vitro* (page 576, col 3, para 1 and 3).

Thus a high degree of unpredictability is associated with the use of antisense constructs employed in methods of inhibiting expression of a particular protein in an animal model and these problems would also be expected to be found in the human condition as contemplated by the specification.

In addition, the state of the art at the time of filing was that the combination of vector, promoter, protein, cell, target tissue, level of expression and route of administration required to target the tissue of interest and obtain a therapeutic effect using gene therapy was unpredictable. For example, Miller (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion

section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

In view of the above, it would be undue experimentation for one of skill in the art at the time the invention was made to practice the claimed invention.

D. If Applicant could overcome the above 112, first paragraph, claims 1-5, are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polynucleotide of SEQ ID NO:1, encoding a Chfr protein of SEQ ID NO:2, which inhibits the transition of cells from prophase to metaphase, **does not reasonably provide enablement for a nucleic acid sequence encoding a Chfr protein, wherein said protein is required for "regulation" of the transition of cells from prophase to metaphase**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims

Claims 1-5 are drawn to a nucleic acid sequence encoding a Chfr protein, wherein said protein is required for "regulation" of the transition of cells from prophase to metaphase.

It is noted that "regulation" of the transition of cells from prophase to metaphase encompasses either enhancing or inhibiting the transition of cells from prophase to metaphase.

The specification discloses that SEQ ID NO:2, encoded by the claimed polynucleotide of SEQ ID NO:1 inhibits the transition of cells from prophase to metaphase. There is no indication that SEQ ID NO:2 could enhance the transition of cells from prophase to metaphase.

In view of the above, it would be undue experimentation for one of skill in the art at the time the invention was made to practice the claimed invention.

REJECTION UNDER 35 USC 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 2 is rejected under 35 U.S.C. 102(b) as being anticipated by Boehringer Mannheim Biochemicals, 1994 Catalog, p. 93.

Claim 2 is drawn to an antisense sequence of SEQ ID NO:1, a sequence encoding at least amino acids 31-103, and/or amino acids 303 –346, and/or amino acids 476-641.

The Boehringer Mannheim teaches a kit comprising random primers that encompass all possible 6-nucleotide sequences (see page 93, Catalog No. 1034 731/1006 924).

Given the polynucleotide sequences taught by Boehringer Mannheim, one of ordinary skill in the art would immediately envision the claimed antisense sequence.

REJECTION UNDER 35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1. Claims 21, 23, 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO20021991-A1 in view of Sambrook et al, 1989, Molecular cloning, a Laboratory manual, 2nd ed, Cold spring Harbor Laboratory Press, Cold Spring Harbor, p.10.6-10.7.

Claims 21, 23, 25 are drawn to a diagnostic reagent or kit comprising a nucleotide sequence that binds to the Chfr nucleic acid sequence or a fragment thereof, or a ligand that binds to Chfr, said reagent or ligand is associated with a detectable label.

Claims 21, 23, 25 recite the claimed reagent or kit, formulated as a diagnostic reagent or kit. However, this limitation is viewed as a recitation of intended use and

therefore is not given patentable weight in comparing the claims with the prior art. Claims 21, 23, 25 read on the ingredient per se, which is a reagent or a kit comprising a nucleotide sequence that binds to the Chfr nucleic acid sequence or a fragment thereof, or a ligand that binds to Chfr, said reagent or ligand is associated with a detectable label.

WO20021991-A1 teaches a sequence, SEQ ID NO:911, which is 100% similar to SEQ ID NO:1, from nucleotide 876 to nucleotide 1161, as shown by MPSRCH search (MPSRCH search report, 2004, us-10-048-046-1.oligo.rng, pages18-19).

Although WO20021991-A1 does not teach that the sequence binds to the chfr nucleic acid sequence, however, one would have expected that the sequence taught by WO20021991-A1 would bind to the chfr nucleic acid sequence or SEQ ID NO:1, in view of the extensive homology of the sequence taught by WO20021991-A1 with SEQ ID NO:1 (See the above MPSRCH search report).

WO20021991-A1 does not teach a detectable label.

Sambrook et al teach labeling of DNA probes by nick translation (p.10.6-10.7).

It would have been prima facia obvious for one of ordinary skill in the art at the time the invention was made to label the nucleic acid sequence taught by WO20021991-A1, using the method of Sambrook et al, for detecting the presence of the nucleic acid sequence for diagnosis purpose. Further, it would have been obvious to formulate the polynucleotide sequence taught by WO20021991-A1 as a kit in order to have standardization for tests to characterize the polynucleotide sequence for commercial application.

2. Claims 21-23, 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boehringer Mannheim Biochemicals, supra, in view of Sambrook et al, 1989, Molecular cloning, a Laboratory manual, 2nd ed, Cold spring Harbor Laboratory Press, Cold Spring Harbor, p.10.6-10.7.

Claims 21-23, 25 are drawn to a diagnostic reagent or kit comprising a nucleotide sequence that binds to the Chfr nucleic acid sequence or a fragment thereof, or a ligand that binds to Chfr, said reagent or ligand is associated with a detectable label. Said reagent of claim 21 is an antisense fragment or a fragment of SEQ ID NO:1.

Claims 21, 23, 25 recite the claimed reagent or kit, formulated as a diagnostic reagent or kit. However, this limitation is viewed as a recitation of intended use and therefore is not given patentable weight in comparing the claims with the prior art. Claims 21, 23, 25 read on the ingredient per se, which is a reagent or a kit comprising a nucleotide sequence that binds to the Chfr nucleic acid sequence or a fragment thereof, or a ligand that binds to Chfr, said reagent or ligand is associated with a detectable label.

The teaching of Boehringer Mannheim Biochemicals has been set forth above.

Although Boehringer Mannheim Biochemicals does not teach that the sequence binds to the chfr nucleic acid sequence, however, one would have expected that the sequence taught by Boehringer Mannheim Biochemicals would bind to the chfr nucleic acid sequence or SEQ ID NO:1.

Boehringer Mannheim Biochemicals does not teach a detectable label.

Sambrook et al teach labeling of DNA probes by nick translation (p.10.6-10.7).

It would have been prima facia obvious for one of ordinary skill in the art at the time the invention was made to label the sequence taught by Boehringer Mannheim Biochemicals, using the method of Sambrook et al, for detecting the presence of nucleic acid sequence. Further, it would have been obvious to formulate the sequence taught by Boehringer Mannheim Biochemicals as a kit as taught by Boehringer Mannheim Biochemicals or as a reagent for commercial application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, CHRISTINA CHAN can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

MINH TAM DAVIS

May 20, 2004